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Electrophilic fluorocyclization of unsaturated alcohols in ionic liquids

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ABSTRACT

Fluorocyclization of phenyl-substituted alkenols in ionic liquids under action of N–F reagents namely F-TEDA-BF_4 and *N*-fluorobenzenesulfonimide has been studied. Opposite to the non-stereoselective reaction in organic solvents the reaction in ionic liquids resulted in the formation preferably of the *trans*-diastereomeric fluorinated cyclic ethers. 2-Difluoromethyl-2-phenyl-tetrahydrofuran was obtained by interaction of 4-phenylpent-4-en-1-ol with F-TEDA-BF_4 in ionic liquids.

1. Introduction

Tetrahydrofuran and tetrahydropyran rings are the key structural unit in a large group of natural products known as polyether antibiotics,[1,2] acetogenis[3] and *C*-glycosides.[4] Extensive researches have been carried out to develop the stereo-selective synthesis of fluorinated cyclic ethers since they can exhibit specific biological activity. For instance, some organofluorine compounds with a fluorinated furan ring reveal anti-HIV (human immunodeficiency virus) and anticancer activities.[5–7]

The fluorinated cyclic ethers were synthesized via cyclization of fluoro alcohols[8,9] or by fluorination of cyclic ethers.[10,11] However, these methods do not secure the stereoselectivity or require a multi-step procedure. One-pot preparation of fluorinated tetrahydrofurans and tetrahydropyrans by means of electrophilic fluorocyclization of unsaturated alcohols is still challenging. There are only few reports dealing with the synthesis of fluorinated tetrahydrofuran derivatives and other cyclic compounds. The fluorocyclization of unsaturated alcohols under action of iodotoluene difluoride in the presence of various HF–amine complexes in CH_2Cl_2[12] and *N*-fluoropentachloropyridinium triflate in acetonitrile[13] results in moderate yields of the products and poor stereoselectivity. Stereoselective fluoroetherification of homoallylic alcohols to fluorinated tetrahydrofurans was successfully carried out using N–F electrophilic fluorinating reagents. But this method requires prior introduction bulky silyl groups in the starting unsaturated alcohols to activate the double bond.[14] Recently Gouverneur and co-workers have described the organocatalyzed enantioselective fluorocyclization of substituted indolylethanoles induced by N–F reagents that gives mainly *cis*-diastereomeric tetrahydrofuroindoles.[15] These cyclizations were effectively performed at room and low (−78 °C) temperatures in acetone or acetonitrile due to the reactive enamine double bond of the indoles and the use of cinchona alkaloids as organocatalysts.

Here we are presenting the results dealing with the application of ionic liquids (ILs) as a reaction media for cyclization reactions induced by N–F electrophilic reagents. It is known that use of ILs can improve the reaction rate and selectivity of various organic reactions.[16–18] However there are only a few data reported about the influence of ILs on the product yield, regio- and stereoselectivity in the case of fluorination of unsaturated compounds. Fluorination of 3-methylindole with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4) in ILs as reaction media results in the formation of fluorinated products in a good yield and high chemoselectivity.[19] Recently we have shown that fluorolactonization of unsaturated carboxylic acids under action of F-TEDA-BF_4 in ILs proceed faster and provide a better stereoselectivity in comparison to acetonitrile as reaction media.[20]

In this study, we present the influence of IL media on the selectivity and efficiency of the fluorocyclization of alkenols in comparison to common organic solvents. The fluorocyclization of

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trans-5-phenylpent-4-en-1-ol (**1a**), *trans*-4-phenylbut-3-en-1-ol (**2a**), *cis*-5-phenylpent-4-en-1-ol (**1b**), *cis*-4-phenylbut-3-en-1-ol (**2b**) and 4-phenylpent-4-en-1-ol (**3**) with F-TEDA-BF4 and *N*-fluorobenzenesulfonimide (NFSI) was carried out in hydrophilic ILs, such as 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF_4]), 1-ethyl-3-methylimidazolium triflate ([emim][CF_3SO_3]), 1-butyl-3-methylpyrrolidinium triflate ([bmpyr][CF_3SO_3]), and in hydrophobic ILs, such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), 1-ethyl-3-methylimidazolium bis(trifluoromethylsulphonyl)imide ([emim][$(CF_3SO_2)_2N$]) and 1-butyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate ([bmim][$(C_2F_5)_3PF_3$]).

2. Results and discussion

The fluorocyclization of alkenol **1a** with F-TEDA-BF_4 and NFSI in hydrophilic ILs and organic solvents (nitromethane, nitroethane and acetonitrile) leads to the formation of fluorinated *trans*-(**4**) and *cis*-tetrahydropyrans (**5**) in average yields of about 75% (Table 1). It was found out that ILs strongly influence the stereoselectivity of fluorocyclization reactions. The *trans*-fluorotetrahydropyran **4** was preferably formed in ILs as reaction media. The ratio **4**/**5** was equal to 7.1 when alkenol **1a** reacted with F-TEDA-BF_4 in [emim][CF_3SO_3] (Table 1, entry 2). Similar stereoselectivity (the ratio **4**/**5** is 5.9) was observed in [bmpyr][CF_3SO_3] (Table 1, entry 3). To our surprise, the reaction of the alkenol **1a** with F-TEDA-BF_4 in hydrophobic IL [bmim][PF_6] gave a lot of tar, and resulted in the formation of the fluorotetrahydropyrans **4** and **5** only in the yield of about 10%. Similar decrease of the reaction rate in [bmim][PF_6], in comparison to [bmim][BF_4], was observed in the reaction of 1,1-diphenyl ethylene with F-TEDA-BF_4 in the presence of nucleophiles.[21] The very low fluorocyclization rate can be explained by the lack of solvation of the hydroxy group in hydrophobic IL that does not support deprotonation of the intermediate **A** (Table 1) and consequently the occurring of the cyclization. Moreover, a reaction of hydrolytically unstable [bmim][PF_6][22] with residual water (moisture) and presumably with the alkenol **1a** (in particular at elevated temperature) resulting in the formation of HF, which can cause severe tarring of the reaction mixture. Furthermore, the high viscosity of [bmim][PF_6] (450 cP)[23] may influence the reaction rate as well. On the contrary, hydrolytically stable and less viscous [bmim][CF_3SO_3] (90 cP) and [emim][BF_4] (43 cP)[23] provide better conditions for the fluorocyclization of the alkenol **1a**.

In comparison to the reaction in ILs the fluorocyclization of the alkenol **1a** with F-TEDA-BF_4 at 80 °C in organic solvents, such as nitromethane, nitroethane and acetonitrile proceeds non-selectively. The ratio **4**/**5** in all these cases varies between 1.0 and 1.2 (Table 1, entries 5, 7, 9).

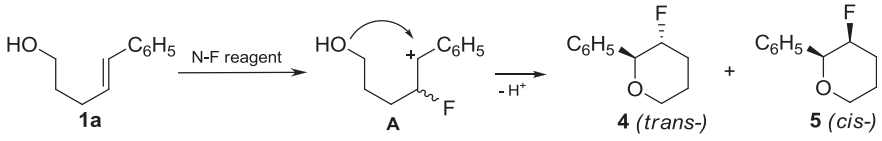
It is important to note, if the fluorocyclization of the alkenol **1a** under action of F-TEDA-BF_4 was carried out in nitromethane at room temperature the *cis*-diastereomer **5** was preferably formed; the ratio **4**/**5** is equal to 0.3 (Table 1, entry 6). Heating of this reaction mixture (Table 1, entry 6) to 80 °C did not change the ratio of the products **4** and **5**, confirming that the products **4** and **5** were formed under kinetic control.

The fluorocyclization of the alkenol **1a** in nitromethane and nitroethane proceeds much faster than in acetonitrile or ILs (Table 1, entries 1–7, 9). We believe, that higher reaction rate in nitroalkanes is due to the high C–H acidity of nitromethane (pK_a=10.2) and nitroethane (pK_a=8.6) (determined in 50% v/v H_2O/MeOH)[24] by the reason of equilibrium with nitronic acids: RCH=N(O)OH. Reaction of nitronic acid with F-TEDA-BF_4 presumably leads to the formation in situ of a very strong fluorinating reagent, hypofluorite R–CH=N(O)OF. Similar acceleration has been reported by direct fluorination of aromatic substances with F_2 in protic acids, for instance in formic or sulfuric acid.[25] The possible explanation of this phenomenon is in situ formation of a hypofluorite, which rapidly reacts with the substrate.[26] The equilibrium with nitronic acid is not possible in the case of nitrobenzene. As consequence, the fluorocyclization of the alkenol **1a** in nitrobenzene doesn't proceed at all (Table 1, entry 8).

The fluorocyclization of the alkenol **1a** in a mixture of [emim][CF_3SO_3]/CH_3NO_2 (1:1) proceeds much faster than in neat IL, perhaps due to the decrease in the viscosity,[27] and results in the formation of the *trans*-fluorotetrahydropyran **4** with a good stereoselectivity (Table 1, entry 10).

It is known that presence of small amount of water can modify the physical properties of ILs (viscosity, density, etc.) as well as the polarity and structural characterizations of ILs.[23,27] The water molecules are well solubilized in hydrophilic ionic liquids and exist in symmetrical 1:2 type H-bonded complexes: anion···H–O–H···anion. This breaks the imidazolium–imidazolium association and the

Table 1
Fluorocyclization of *trans*-5-phenylpent-4-en-1-ol (**1a**) in ILs and organic solvents



Entry	N–F reagent	*T*, °C	Time, h	Reaction's media	Yield[a] (**4**+**5**), %	*trans* (**4**)/*cis* (**5**)[c]
1	F-TEDA-BF_4	80	32	[emim][BF_4]	75	3.8
2	F-TEDA-BF_4	80	40	[emim][CF_3SO_3]	77/58[b]	7.1
3	F-TEDA-BF_4	80	45	[bmpyr][CF_3SO_3]	76	5.9
4	F-TEDA-BF_4	80	40	[bmim][PF_6]	ca. 10	—
5	F-TEDA-BF_4	80	3	CH_3NO_2	83	1.2
6	F-TEDA-BF_4	20	48	CH_3NO_2	72	0.3
7	F-TEDA-BF_4	80	5	$C_2H_5NO_2$	80	1.1
8	F-TEDA-BF_4	80	35	$C_6H_5NO_2$	—	—
9	F-TEDA-BF_4	80	20	CH_3CN	73	1.0
10	F-TEDA-BF_4	80	15	[emim][CF_3SO_3]-CH_3NO_2 (1:1)	78	4.8
11	F-TEDA-BF_4	80	10	[emim][CF_3SO_3]-H_2O (1.95:0.14)	73	3.7
12	F-TEDA-BF_4	80	32	[emim][$(CF_3SO_2)_2N$]	75	3.1
13	NFSI	80	32	[emim][CF_3SO_3]	77	2.1

[a] Yields were determined by ^{19}F NMR.
[b] Isolated yields after column chromatography.
[c] *trans*/*cis* ratios were estimated by ^{19}F NMR.